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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,729	11/17/2003	Jean-Pierre Sommadossi	11874-064-999 (IDX 1022)	5135

20583 7590 12/23/2008

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222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,729	SOMMADOSSI ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34,38-40,87,89,92,101,103-107 and 109-122* is/are pending in the application.

4a) Of the above claim(s) *38 and 87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,39,40,89,92,101,103-107 and 109-122* is/are rejected.

7)☒ Claim(s) *107* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 September 2008 has been entered.

DETAILED ACTION

This Office Action is in response to the amendment filed 26 September 2008. Claims 1-32, 35-37, 41-86, 88, 90, 91, 93-100, 102, and 108 have been cancelled. Claims 109-122 have been added. Claims 33, 34, 38-40, 87, 89, 92, 101, 103-107 and 109-122 are pending. Claims 38 and 87 are withdrawn. Claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 are currently examined.

Claim Objections

Claim 107 is objected to because of a grammatical error in the phrase "the method of any one of claim 33." Applicants may consider deleting the phrase "any one of" from the claim language. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15 and 16 of U.S. Patent No. 7,169,766B2 in view of Arens *et al.* (2001).

The instant claims are drawn to a method for treating a hepatitis C virus infection in a host, comprising (a) administering an effective amount of a 2'-branched nucleoside or a pharmaceutically acceptable prodrug or salt thereof to the host; (b) identifying viral resistance to the 2'-branched nucleoside in the host; and (c) administering to the host, who is infected with the virus resistant to the 2'- branched nucleoside, an effective amount of one or more drugs that directly or indirectly induce a mutation in a hepatitis C virus at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence,

XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region. Such a drug is more specifically limited to interferon.

The patented claims are drawn to a method for the treatment of a hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a beta-D-2'-branched nucleoside compound or a pharmaceutically acceptable salt or ester thereof in combination or alternation with a second agent, especially an interferon.

The patent claims differ from the instant claims in that they do not recite the step of identifying viral resistance to the 2'-branched nucleoside in the host.

Arens *et al.* discloses that HCV can be treated by the combination of interferon and ribavirin but certain strains of virus are more resistant to treatment than others and suggests that genotyping of HBV, HCV, CMV, and HIV is important to the therapeutic regimen (Abstract). Specifically for HBV, Arens suggests drug susceptibility testing comprising a genotype assay detecting mutations in the genome that may confer drug resistance and a phenotypic assay measuring replication fitness, which is the actual ability of the virus to grow in the presence of various chemical compounds or known antiviral drugs (page 12, right column). As a general genotyping approach for all of the viruses but as an example for genotyping/phenotyping CMV, DNA is extracted from whole blood (page 21, right column, second paragraph) and the phenotypic analysis is done by plaque reduction assay (page 21, right column, first paragraph). More specifically, Arens suggests different genotyping methods including sequencing, primer-specific PCR and hybridization that can detect mutations at certain locations within a specific genome (page 13, left column, first paragraph).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the HCV treatment method in the claims of US Patent No. 7,169,766 B2 so as to add the step of identifying viral resistance to the 2'-branched nucleoside in the host with a reasonable expectation of success because Arens suggests that the determination of HCV genotype and evaluating the viral phenotype is important to the regimen. One having ordinary skill in the art would have been motivated to modify the Carroll method to determine the efficacy of the 2'-branched nucleoside and to identify the clinical outcome associated with the interferon alone or the combination of the 2'-branched nucleoside with interferon, as per the teachings of Arens *et al.*

Claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-7, 9, 12, 13 and 17 of U.S. Patent No. 7,192,936B2 in view of Arens *et al.* (2001).

The instant claims are drawn to a method for treating hepatitis C virus infection in a host, comprising (a) administering an effective amount of a 2'-branched nucleoside or a pharmaceutically acceptable prodrug or salt thereof to the host; (b) identifying viral resistance to the 2'-branched nucleoside in the host; and (c) administering to the host, who is infected with the virus resistant to the 2'- branched nucleoside, an effective amount of one or more drugs that directly or indirectly induce a mutation in a hepatitis C virus at a location other than a mutation of a nucleotide that results in a change from

serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region. Such a drug is more specifically limited to interferon.

The patented claims are drawn to a method for the treatment of a Flaviviridae virus infection, specifically limited to a hepatitis C virus infection, in a host, comprising administering an anti-virally effective amount of a -2'-branched nucleoside compound or a pharmaceutically acceptable salt or ester thereof in combination or alternation with a second agent, especially an interferon.

The patent claims differ from the instant claims in that they do not recite the step of identifying viral resistance to the 2'-branched nucleoside in the host.

Arens *et al.* discloses that HCV can be treated by the combination of interferon and ribavirin but certain strains of virus are more resistant to treatment than others and suggests that genotyping of HBV, HCV, CMV, and HIV is important to the therapeutic regimen (Abstract). Specifically for HBV, Arens suggests drug susceptibility testing comprising a genotype assay detecting mutations in the genome that may confer drug resistance and a phenotypic assay measuring replication fitness, which is the actual ability of the virus to grow in the presence of various chemical compounds or known antiviral drugs (page 12, right column). As a general genotyping approach for all of the viruses but as an example for genotyping/phenotyping CMV, DNA is extracted from whole blood (page 21, right column, second paragraph) and the phenotypic analysis is done by plaque reduction assay (page 21, right column, first paragraph). More specifically, Arens suggests different genotyping methods including sequencing, primer-

specific PCR and hybridization that can detect mutations at certain locations within a specific genome (page 13, left column, first paragraph).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the HCV treatment method in the claims of US Patent No. 7,169,766 B2 so as to add the step of identifying viral resistance to the 2'-branched nucleoside in the host with a reasonable expectation of success because Arens suggests that the determination of HCV genotype and evaluating the viral phenotype is important to the regimen. One having ordinary skill in the art would have been motivated to modify the Carroll method to determine the efficacy of the 2'-branched nucleoside and to identify the clinical outcome associated with the interferon alone or the combination of the 2'-branched nucleoside with interferon, as per the teachings of Arens *et al.*

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> The changes made to 35 U.S.C. §102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. §102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. §102(e)).

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of claims 33, 34, 92, 104 and 107 under 35 U.S.C. §102(e) as being anticipated by Carroll *et al.* (US 7,105,499 B2) is **withdrawn** in response to Applicant's amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 39, 40, 89, 101, 103, 105 and 106 under 35 U.S.C. §103(a) as being obvious over Carroll *et al.* (US 7,105,499 B2) in view of Sinko *et al.* (1998) is **withdrawn** in response to Applicants' amendment.

New Grounds of Rejection

Claims 33, 34, 92, 104, 107 and 109-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carroll *et al.* (US 7,105,499 B2, priority filing date 22 January 2001, hereinafter "Carroll") in view of Arens *et al.* (2001, hereinafter "Arens").

The instant claims are drawn to a method for treating a hepatitis C virus infection in a host, comprising (a) administering an effective amount of a 2'-branched nucleoside

or a pharmaceutically acceptable prodrug or salt thereof to the host; (b) identifying viral resistance to the 2'-branched nucleoside in the host; and (c) administering to the host, who is infected with the virus resistant to the 2'- branched nucleoside, an effective amount of one or more drugs that directly or indirectly induce a mutation in a hepatitis C virus at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region.

Carroll discloses a method of treating RNA-dependent RNA viral infection or an HCV infection, by administering a compound such as 2'-methyl-cytidine (column 15, line 14-67), in combination or alternation with other agents like ribavirin, viramidine, levovirin, thymosin alpha-1, HCV NS3 serine protease inhibitor, interferon-a-2b (column 32), VX-497, mycophenolate mofetil, amantadine and 2'-C-branched ribonucleosides (column 33), in association with a pharmaceutically acceptable carrier (column 2, lines 54-57). The HCV NS3 serine protease inhibitor and interferon are drugs that directly or indirectly induce a mutation in a HCV at a location other than the serine in the XRXSGXXXT sequence of RNA polymerase B region.

Carroll does not disclose step (b) of identifying viral resistance.

Arens *et al.* discloses that HCV can be treated by the combination of interferon and ribavirin but certain strains of virus are more resistant to treatment than others and suggests that genotyping of HBV, HCV, CMV, and HIV is important to the therapeutic regimen (Abstract). Specifically for HBV, Arens suggests drug susceptibility testing comprising a genotype assay detecting mutations in the genome that may confer drug

resistance and a phenotypic assay measuring replication fitness, which is the actual ability of the virus to grow in the presence of various chemical compounds or known antiviral drugs (page 12, right column). As a general genotyping approach for all of the viruses but as an example for genotyping/phenotyping CMV, DNA is extracted from whole blood (page 21, right column, second paragraph) and the phenotypic analysis is done by plaque reduction assay (page 21, right column, first paragraph). More specifically, Arens suggests different genotyping methods including sequencing, primer-specific PCR and hybridization that can detect mutations at certain locations within a specific genome (page 13, left column, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Carroll method so as to add the step of identifying viral resistance to the 2'-branched nucleoside in the host with a reasonable expectation of success because Arens suggests that the determination of HCV genotype and evaluating the viral phenotype is important to the regimen. One would be motivated to modify the Carroll method to determine the efficacy of the 2'-branched nucleoside and to identify the clinical outcome associated with the interferon alone or the combination of the 2'-branched nucleoside with interferon. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carroll *et al.* (US 7,105,499 B2, priority filing

date 22 January 2001, hereinafter "Carroll") in view of Arens *et al.* (2001, hereinafter "Arens") and Sinko *et al.* (1998, hereinafter "Sinko").

The instant invention is further limited to a valinyl ester prodrug of the 2'-branched pyrimidine.

The relevance of Carroll and Arens is set forth above. Carroll and Arens do not disclose an amino acid ester prodrug.

Sinko discloses valacyclovir (VACV), the L-valyl ester of the acyclic nucleoside analog of deoxyguanosine. Sinko suggests that L-valyl ester prodrug demonstrates an oral availability that is 3-5 times greater than acyclovir, concentration dependent, and saturable in humans (Abstract). Sinko further discloses that the mean absolute oral bioavailability of VACV is three to five times that of acyclovir in humans. See page 209, right column, second paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Carroll method so as to replace the 3'-OH group of 2'-branched nucleoside with a valine ester group to make a valinyl ester prodrug with a reasonable expectation of success because Sinko teaches that a valinyl ester prodrug can enhance the oral bioavailability of the nucleoside drug and improve the intestinal uptake of nucleoside analog acyclovir. One would be motivated to improve the oral availability of the 2'-branched nucleoside by making it more saturable in humans as suggested by Sinko. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648
16 December 2008
/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648

UNITED STATES PATENT AND TRADEMARK OFFICE

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20583 7590 07/07/2009

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	LOUISE HUMPHREY	1648	

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Status

1)☒ Responsive to communication(s) filed on *22 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34,38-40,87,89,92,101,103-107 and 109-122* is/are pending in the application.

4a) Of the above claim(s) *38 and 87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,39,40,89,92,101,103-107 and 109-122* is/are rejected.

7)☒ Claim(s) *107* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

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11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/22/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 22 April 2009. Claims 1-32, 35-37, 41-86, 88, 90, 91, 93-100, 102 and 108 have been cancelled. Claims 33, 34, 38-40, 87, 89, 92, 101, 103-107 and 109-122 are pending. Claims 38 and 87 are drawn to a nonelected subject matter and hence are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 are currently examined.

Claim Objections

The objection to claim 107 is maintained. Applicants did not respond to the objection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The nonstatutory double patenting rejection of claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 as being unpatentable over claims 15 and 16 of US Patent No. 7,169,766 B2 (hereinafter '766) in view of Arens *et al.* (2001, hereinafter "Arens") is **maintained**.

The instant claims are drawn to a method for treating a hepatitis C virus infection in a host, comprising (a) administering an effective amount of a 2'-branched pyrimidine or a pharmaceutically acceptable prodrug or salt thereof to the host; (b) identifying viral resistance to the 2'-branched nucleoside in the host; and (c) administering to the host, who is infected with the virus resistant to the 2'- branched nucleoside, an effective amount of one or more drugs that directly or indirectly induce a mutation in a hepatitis C virus at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region. Such a drug is more specifically limited to interferon.

The patented claims are drawn to a method for the treatment of a hepatitis C virus infection in a host, comprising administering an anti-virally effective amount of a beta-D-2'-branched nucleoside compound or a pharmaceutically acceptable salt or ester thereof in combination or alternation with a second agent, especially an interferon.

The patent claims differ from the instant claims in that they do not recite the step of identifying viral resistance to the 2'-branched nucleoside in the host.

Arens discloses that HCV can be treated by the combination of interferon and ribavirin but certain strains of virus are more resistant to treatment than others and suggests that genotyping of HBV, HCV, CMV, and HIV is important to the therapeutic regimen (Abstract). Specifically for HBV, Arens suggests drug susceptibility testing comprising a genotype assay detecting mutations in the genome that may confer drug resistance and a phenotypic assay measuring replication fitness, which is the actual ability of the virus to grow in the presence of various chemical compounds or known antiviral drugs (page 12, right column). As a general genotyping approach for all of the viruses but as an example for genotyping/phenotyping CMV, DNA is extracted from whole blood (page 21, right column, second paragraph) and the phenotypic analysis is done by plaque reduction assay (page 21, right column, first paragraph). More specifically, Arens suggests different genotyping methods including sequencing, primer-specific PCR and hybridization that can detect mutations at certain locations within a specific genome (page 13, left column, first paragraph).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the HCV treatment method in the claims of US Patent No. 7,169,766 B2 so as to add the step of identifying viral resistance to the 2'-branched nucleoside in the host with a reasonable expectation of success because Arens suggests that the determination of HCV genotype and evaluating the viral phenotype is important to the regimen. One having ordinary skill in the art would have been motivated to modify the patent method to determine the efficacy of the 2'-branched nucleoside and to identify the clinical outcome associated

with the interferon alone or the combination of the 2'-branched nucleoside with interferon, as per the teachings of Arens.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue that the '766 patent claims only combination therapy with 2'-C-branched triazolopyridine, imidazolopyridine, or pyrazolopyrimidine without the mention of the identification of viral resistance. Examiner has acknowledged the missing claim limitation of identification of viral resistance in the '766 patent in the previous Office Action and has cited the secondary reference, Arens. As Applicants conceded, the '766 patent claims combination therapy with 2'-branched pyrazolopyrimidine, which is encompassed by the instant claim limitation of 2'-branched pyrimidine nucleoside.

Applicants further argue that Arens does not teach the identification of HCV resistance to 2'-C-branched nucleosides and the combination of the claimed 2'-C-branched pyrimidine nucleosides with drugs that induce a mutation in the virus at a location other than an amino acid mutation in the highly conserved sequence recited in claim 33. The claim limitation of the combination of 2'-branched pyrimidine nucleosides with drugs that induce a mutation in the virus at a location other than an amino acid mutation in the highly conserved sequence of domain B of the RNA polymerase region is clearly recited in the patent claims 15 and 16, which direct the second drug to interferon, which is clearly recited in the instant claims.

Examiner does not concur with Applicants' argument that Arens does not teach a general genotyping approach to all the viruses. Arens clearly discloses HCV as one of the four human viruses for which genotype information is clinically useful (Abstract and page 14, left column) and that genotyping refers to characterization of all or part of a viral genome with regards to the presence of mutations, as compared to a reference or wild type strain of the same organism (page 12, left column, first paragraph), that may confer drug resistance (page 12, right column, first sentence).

Applicants further argue that Arens teaches away from the instant claims because it teaches that viral resistance cannot be evaluated absent knowledge of the location of a specific HCV mutation and the locations are not disclosed. Examiner respectfully disagrees based on the common knowledge in the art of antiviral drug resistance that the location of resistance-conferring mutations coincides with the drug binding site, which is in the RNA polymerase region for the claimed 2'-branched pyrimidine nucleosides. It is the most common drug-evasion mechanism that mutations of amino acid residues lining the drug binding sites affect the drug binding affinity and thereby reduces the drug efficacy. Since the patent claims recite the drug, 2'-branched pyrimidine nucleoside, a well known substrate for a polymerase, one skilled in the art would immediately recognize that the drug binding site is the HCV RNA polymerase, NS5B, and thus the location of mutations that confer resistance is known for the genotype analysis for resistance testing.

Finally, Applicants argue that Arens admits to difficulty in identifying accurate genotype data for HCV. However, this portion of the reference pertains to determining

the type or subtype of the viruses and is not germane to the rejection at issue, which only concerns viral drug resistance testing.

The provisional nonstatutory double patenting rejection of 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 as being unpatentable over claims 2-7, 9, 12, 13 and 17 of US Patent No. 7,169,766 B2 (hereinafter '766) in view of Arens *et al.* (2001, hereinafter "Arens") is **maintained**.

The instant claims are drawn to a method for treating hepatitis C virus infection in a host, comprising (a) administering an effective amount of a 2'-branched pyrimidine nucleoside or a pharmaceutically acceptable prodrug or salt thereof to the host; (b) identifying viral resistance to the 2'-branched nucleoside in the host; and (c) administering to the host, who is infected with the virus resistant to the 2'- branched nucleoside, an effective amount of one or more drugs that directly or indirectly induce a mutation in a hepatitis C virus at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region. Such a drug is more specifically limited to interferon.

The patented claims are drawn to a method for the treatment of a Flaviviridae virus infection, specifically limited to a hepatitis C virus infection, in a host, comprising administering an anti-virally effective amount of a -2'-branched nucleoside compound or a pharmaceutically acceptable salt or ester thereof in combination or alternation with a second agent, especially an interferon.

The patent claims differ from the instant claims in that they do not recite the step of identifying viral resistance to the 2'-branched nucleoside in the host.

Arens *et al*. discloses that HCV can be treated by the combination of interferon and ribavirin but certain strains of virus are more resistant to treatment than others and suggests that genotyping of HBV, HCV, CMV, and HIV is important to the therapeutic regimen (Abstract). Specifically for HBV, Arens suggests drug susceptibility testing comprising a genotype assay detecting mutations in the genome that may confer drug resistance and a phenotypic assay measuring replication fitness, which is the actual ability of the virus to grow in the presence of various chemical compounds or known antiviral drugs (page 12, right column). As a general genotyping approach for all of the viruses but as an example for genotyping/phenotyping CMV, DNA is extracted from whole blood (page 21, right column, second paragraph) and the phenotypic analysis is done by plaque reduction assay (page 21, right column, first paragraph). More specifically, Arens suggests different genotyping methods including sequencing, primer-specific PCR and hybridization that can detect mutations at certain locations within a specific genome (page 13, left column, first paragraph).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the HCV treatment method in the claims of US Patent No. 7,169,766 B2 so as to add the step of identifying viral resistance to the 2'-branched nucleoside in the host with a reasonable expectation of success because Arens suggests that the determination of HCV genotype and evaluating the viral phenotype is important to the regimen. One having ordinary skill in

the art would have been motivated to modify the Carroll method to determine the efficacy of the 2'-branched nucleoside and to identify the clinical outcome associated with the interferon alone or the combination of the 2'-branched nucleoside with interferon, as per the teachings of Arens.

Response to Arguments

Applicants proffered the same arguments against both references, which are not persuasive for the same reasons as set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 33, 34, 92, 104, 107 and 109-122 under 35 U.S.C. §103(a) as being obvious over Carroll *et al.* (US 7,105,499 B2, priority filing date 22 January 2001, hereinafter "Carroll") in view of Arens *et al.* (2001, hereinafter "Arens") is **maintained**.

The instant claims are drawn to a method for treating a hepatitis C virus infection in a host, comprising (a) administering an effective amount of a 2'-branched nucleoside or a pharmaceutically acceptable prodrug or salt thereof to the host; (b) identifying viral resistance to the 2'-branched nucleoside in the host; and (c)

administering to the host, who is infected with the virus resistant to the 2'- branched nucleoside, an effective amount of one or more drugs that directly or indirectly induce a mutation in a hepatitis C virus at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region.

Carroll discloses a method of treating RNA-dependent RNA viral infection or an HCV infection, by administering a compound such as 2'-methyl-cytidine (column 15, line 14-67), a 2'-branched pyrimidine nucleoside, in combination or alternation with other agents like ribavirin, viramidine, levovirin, thymosin alpha-l, HCV NS3 serine protease inhibitor, interferon-a-2b (column 32), VX-497, and 2'-C-branched ribonucleosides (column 33), in association with a pharmaceutically acceptable carrier (column 2, lines 54-57). The HCV NS3 serine protease inhibitor and interferon are drugs that directly or indirectly induce a mutation in a HCV at a location other than the serine in the XRXSGXXXT sequence of RNA polymerase B region because they do not bind and inhibit RNA polymerase B region.

Carroll does not disclose step (b) of identifying viral resistance.

Arens *et al.* discloses that HCV can be treated by the combination of interferon and ribavirin but certain strains of virus are more resistant to treatment than others and suggests that genotyping of HBV, HCV, CMV, and HIV is important to the therapeutic regimen (Abstract). Specifically for HBV, Arens suggests drug susceptibility testing

comprising a genotype assay detecting mutations in the genome that may confer drug resistance and a phenotypic assay measuring replication fitness, which is the actual ability of the virus to grow in the presence of various chemical compounds or known antiviral drugs (page 12, right column). As a general genotyping approach for all of the viruses but as an example for genotyping/phenotyping CMV, DNA is extracted from whole blood (page 21, right column, second paragraph) and the phenotypic analysis is done by plaque reduction assay (page 21, right column, first paragraph). More specifically, Arens suggests different genotyping methods including sequencing, primer-specific PCR and hybridization that can detect mutations at certain locations within a specific genome (page 13, left column, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Carroll method so as to add the step of identifying viral resistance to the 2'-branched nucleoside in the host with a reasonable expectation of success because Arens suggests that the determination of HCV genotype and evaluating the viral phenotype is important to the regimen. One would be motivated to modify the Carroll method by adding the step to determine the resistance of the 2'-branched pyrimidine nucleoside, by genotyping its HCV target, the NS5B polymerase enzyme, specifically, in the region that the 2'-branched pyrimidine binds and inhibits, and to identify the clinical outcome associated with the interferon alone or the combination of the 2'-branched nucleoside with interferon. Thus, the invention as a

whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that Arens fails to teach the combination of 2'-C-branched nucleosides with drugs that induce a mutation in the virus at a location other than an amino acid mutation in the highly conserved sequence recited in claim 33. However, this argument mischaracterizes the rejection because Carroll was offered for teaching the claimed steps of administering 2'-branched pyrimidine followed by administering a non-polymerase-inhibitor that does not induce a mutation in the HCV RNA polymerase domain B.

Secondly, Applicant argues that Arens does not teach that genotyping would be useful in the specific combination therapy of claim 33 and that Arens does not teach a general genotyping approach to all the viruses discussed therein. Examiner does not concur. Arens explicitly suggests that genotype analysis should be part of the HCV treatment algorithms in the process (page 18, left column). Arens clearly discloses HCV as one of the four human viruses for which genotype information is clinically useful (Abstract and page 14, left column) and that genotyping refers to characterization of all or part of a viral genome with regards to the presence of mutations, as compared to a reference or wild type strain of the same organism (page 12, left column, first paragraph), that may confer drug resistance (page 12, right column, first sentence).

This disclosure would lead one skilled in the art to understand that genotyping is an effective approach to identify mutations that may confer drug resistance in the HCV genome region encoding the site that the administered drug binds and that genotyping is a reasonable step ensuing the administration of a first drug, a 2'-branched pyrimidine nucleoside to determine drug evasion before the administration of a second drug, such as interferon, that acts with a different cell mechanism and is more susceptible to the nucleoside-resistant strains of HCV.

Thirdly, Applicant argues that Arens discloses that the location of the mutations that confer drug resistance must be known in order to evaluate resistance but the Office has not provided any teaching of these specific HCV mutations. Examiner respectfully disagrees based on the common knowledge in the art of antiviral drug resistance that the location of resistance-conferring mutations coincides with the drug binding site, which is, as recited in the instant claims, in the RNA polymerase region domain B for the claimed 2'-branched pyrimidine nucleosides. It is the most common drug-evasion mechanism that mutations of amino acid residues lining the drug binding sites affect the drug binding affinity and thereby reduces the drug efficacy. Since Carroll discloses the drug, 2'-branched pyrimidine nucleoside, a well known substrate for a polymerase, one skilled in the art would immediately recognize that the drug binding site is the HCV RNA polymerase, NS5B, and thus the location of mutations that confer resistance is known for the genotype analysis for resistance testing.

In response to Applicant's argument that there is no suggestion or motivation in any of the cited documents, the rationale to modify or combine the prior art does not

have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

A step in the obviousness analysis is to "determine whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398,418 (2007). A rejection for obviousness must include "articulated reasoning with some rational underpinning to support the legal conclusion." Id., quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006). The proper question to ask is whether a person of ordinary skill in the art would have seen a benefit to combining the prior art teachings. *KSR*, 550 U.S. at 424. The benefit in this case of combining Arens' genotypic identification of mutations with Carroll's HCV treatment method is to identify drug-resistance-conferring mutations, which in turn indicates the decreased

effectiveness of the 2'-branched pyrimidine nucleoside and justifies the next step of administering a different drug, such as interferon, that acts with a different mechanism on HCV infection.

Moreover, Applicant's summary of the teachings of the approved drugs for treating cytomegalovirus (CMV) and Hepatitis B virus and their induced resistance-conferring mutations is not relevant to the rejection at issue. This information was never relied upon for the rejection at issue to establish the case of prima facie obviousness. Rather, only the portion of the DNA extraction technique demonstrated with CMV is cited to establish a reasonable expectation of success of genotyping HCV because the genetic sequence technique is readily applicable to HCV as suggested by Arens (page 14).

Finally, Applicant argues that Arens admits to the difficulty in identifying accurate genotype data for HCV. However, this argument mischaracterizes the citation of the prior art because this portion of the reference pertains to determining the type or subtype of the viruses and is not germane to the rejection at issue, which only concerns viral drug resistance testing. Identifying the subtype of the HCV strain is a separate matter from identifying drug-resistance-conferring mutations. Classification of a HCV subtype is not relevant to the issue of drug resistance especially when all subtypes of HCV are treated with the same drug. For example, as stated by Arens (page 20, the sentence bridging the two columns), a distinction between subtypes 1a and 1b is not clinically important since all type 1's are treated similarly from a therapeutic perspective.

"The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved." *Kotzab*, 217 F.3d at 1370, 55 USPQ2d at 1317. The suggestion or motivation to modify the reference does not have to be in the references themselves. See MPEP §2142. In this case, the motivation to modify the teachings of the Carroll reference with the suggestions of the Arens reference is immediately apparent to one skilled in the art. Therefore, a *prima facie* case of obviousness is properly established.

The rejection of claims 33, 34, 39, 40, 89, 92, 101, 103-107 and 109-122 under 35 U.S.C. §103(a) as being obvious over Carroll *et al.* (US 7,105,499 B2, priority filing date 22 January 2001, hereinafter "Carroll") in view of Arens *et al.* (2001, hereinafter "Arens") and Sinko *et al.* (1998, hereinafter "Sinko") is **maintained**.

The instant invention is further limited to a valinyl ester prodrug of the 2'-branched pyrimidine.

The relevance of Carroll and Arens is set forth above. Carroll and Arens do not disclose an amino acid ester prodrug.

Sinko discloses valacyclovir (VACV), the L-valyl ester of the acyclic nucleoside analog of deoxyguanosine. Sinko suggests that L-valyl ester prodrug demonstrates an oral availability that is 3-5 times greater than acyclovir, concentration dependent, and saturable in humans (Abstract). Sinko further discloses that the mean absolute oral

bioavailability of VACV is three to five times that of acyclovir in humans. See page 209, right column, second paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Carroll method so as to replace the 3'-OH group of 2'-branched nucleoside with a valine ester group to make a valinyl ester prodrug with a reasonable expectation of success because Sinko teaches that a valinyl ester prodrug can enhance the oral bioavailability of the nucleoside drug and improve the intestinal uptake of nucleoside analog acyclovir. One would be motivated to improve the oral availability of the 2'-branched nucleoside by making it more saturable in humans as suggested by Sinko. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants proffered the same arguments against the Carroll and Arens references, which are not persuasive for the same reasons as set forth above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

25 June 2009